

Serum Phosphate, Serum Calcium and Serum iPTH Levels in Patients with CKD and Risk of Cardiovascular events

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ABSTRACT

Objective: To determine the association between serum phosphorus, serum calcium, and serum iPTH and the occurrence of cardiovascular events in patients with diagnosed chronic kidney disease.

Methodology: A prospective cohort study was conducted at Pir Abdul Qadir Shah Jeelani Institute Of Medical Sciences Gambat, Khairpur Mirs and Jinnah Postgraduate Medical Centre between August 2019 and July 2020. All patients over 18 years of age were eligible to participate in the study. Patients with incomplete data or those who were lost to follow-up were excluded from the study. Mineral metabolism parameters including, serum calcium, Phosphorus, and intact iPTH (iPTH), levels were recorded for all patients. Patients were followed up till the start of August 2020 to record any cardiovascular event. Patients were sub stratified into two groups i.e. with or without a CV event.

Results: The study reported that with the exception of serum calcium, both iPTH and serum phosphorus were significantly associated with occurrence of CV events. iPTH levels had a direct association with CV events with a mean iPTH of 157.34 ± 106.95 pg/ml in patients with CV events versus 108.98 ± 85.63 pg/ml in patients without any CV event ($P=0.0005$). The mean serum phosphorus for the group with CV event was 3.57 ± 0.73 mg/dl which was significantly higher than those without CV events ($P=0.03$).

Conclusion: The current study indicated that serum phosphorus and intact iPTH levels were significantly associated with CV events in patients with CKD.

Keywords: serum phosphorus, serum calcium, serum iPTH, cardiovascular events, chronic kidney disease.

INTRODUCTION

Chronic kidney disease can be defined as a chronic defect in normal functions of the kidney.¹ The kidney is responsible for functions such as regular glomerular filtration rate which is normally between 90 to 120 mL/min² whereas reduced kidney function is considered to be when glomerular filtration rate is at less than 60 mL/min for at a duration of at least 3 months.³ Glomerular filtration mainly refers to the kidney acting as a filter and thus shows the ability of the kidney to filter out blood. Many factors contribute to patients having chronic kidney disease notably chronic hypertension and diabetes have been recognized as one of the main causes of chronic kidney disease.⁴ Other factors include genetics as well as the elderly ageing population as end stage renal disease is more commonly seen in elderly patients due to the increasing number of comorbidities associated with end stage renal disease.⁵ The rising number of patients suffering from end stage renal disease is increasing every year notably in 2017, the rough estimate of the number of patients suffering from chronic kidney disease was 700 million which is approximately 9.2% of the world population and has been labelled as the fifth cause of death.⁶ However, in a developing country like Pakistan, the increasing number of chronic kidney patients can put a major burden on the healthcare system. In a metropolitan

city like Karachi 16.6% of the population was suffering from chronic kidney disease in 2014.⁷ The increasing numbers can also be attributed to lack of awareness, lack of education, lack of equipped facilities for CKD patients and higher risk factors such as cardiovascular diseases, diabetes mellitus, glomerulonephritis and renal stones.⁷

Furthermore, serum phosphate levels in the blood are related to increased cardiovascular events in patients with CKD. Higher serum hyperphosphatemia leads to higher cardiovascular events as well as a higher mortality rate in CKD patients.⁸ Phosphate levels in the blood are not high in healthy individuals however, in patients with CKD, phosphate levels are known to increase earlier than usual such as in some studies it had been reported that if serum phosphate increases by 1-mg/dl the rate of mortality will increase between 5 to 8%.⁹ Similarly the levels of Calcium in the blood stay within the normal range in healthy individuals since it is absorbed by the intestine and the kidney is responsible for its excretion. Parathyroid hormone is an important hormone which helps regulate calcium levels in the blood and is imperative for bone resorption. There has not been any significant increase in cardiovascular events noted with high levels of serum calcium or Parathyroid hormone in patients with chronic kidney disease.¹⁰

More research is required in finding out various factors leading to cardiovascular events in CKD patients.

The current study aimed to determine the association between serum phosphorus, serum calcium, and serum iPTH and the occurrence of cardiovascular events in patients with diagnosed chronic kidney disease.

MATERIALS AND METHODS

A prospective cohort study was conducted at Pir Abdul Qadir Shah Jeelani Institute Of Medical Sciences Gambat, Khairpur Mirs and Jinnah Postgraduate Medical Centre between August 2019 and July 2020. All patients over 18 years of age referred to the outpatient department, nephrology clinic diagnosed with chronic kidney disease with intact iPTH levels determined were eligible to participate in the study. Patients with incomplete data or those who were lost to follow-up were excluded from the study. Patients with active COVID-19 infection were also excluded. Ethical approval was obtained from the respective Institutional Review Board Committees prior to the start of the study. Informed verbal and written consent were procured from eligible participants. Mineral metabolism parameters including, serum calcium, Phosphorus, and intact iPTH (iPTH), levels were recorded for all patients. Patients were followed up till the start of August 2020 to record any cardiovascular event. The primary outcome was cardiovascular (CV) event defined by the incidence of myocardial infarction, cerebrovascular accident (CVA), or death due to a cardiovascular cause during the study period. Complete patient history, cardiovascular history, and renal history were recorded to exclude prior cases of CV events. Significant cardiovascular history was defined as existence of peripheral artery disease, previous myocardial infarction, history of stroke or abdominal aneurysm. Modification of diet in renal disease (MDRD) equation was used to calculate the glomerular filtration rate. Liver function tests were performed to rule out chronic liver disease. The calcium levels were adjusted for plasma albumin. Chemiluminescence microparticle immunoassay was used to quantify intact serum iPTH. Standard therapy for mineral metabolism disorders was granted to patients in accordance with current KDOQI guidelines outlining diet, phosphorus restriction, phosphate binders, 25OHD deficiency treatment, and calcitriol.¹¹ For data analysis, SPSS version 26 was used.

RESULTS

Fifty nine (24.7%) patients with CKD suffered from a CV event during follow-up. The mean age in the group with CV event was 74.3±9.5 years while that in the group without CV event, it was 70.3±10.2 years. The difference was statistically significant (P=0.008). The mean low-density lipoprotein (LDL) cholesterol levels were lower in patients with diagnosed CV events compared to those without (86.13±29.79 vs 96.65±33.63) albeit the difference was statistically insignificant (P=0.094). It was observed that Diabetes Mellitus was significantly associated with the occurrence of cardiovascular events in patients with chronic kidney disease (P=0.04) [Table 1].

Upon assessing the mineral panel, it was found that with the exception of serum calcium, both iPTH and serum phosphorus were significantly associated with occurrence of CV events. iPTH levels had a direct association with CV

events with a mean ± SD iPTH of 157.34 ± 106.95 pg/ml in patients with CV events versus 108.98 ± 85.63 pg/ml in patients without any CV event (P=0.0005). The mean serum phosphorus ± SD for the group with CV event was 3.57 ± 0.73 mg/dl which was significantly higher than those without CV events (P=0.03) [Table 2]

DISCUSSION

With CVS events being the leading cause of mortality in much of the developed world, it is absolutely imperative that healthcare workers are able to deduce associated biomarkers and distinguish causal factors.⁹ Faced with the potential for poorer clinical outcomes in patients with markers associated with enhanced risk, measures may be taken which are better suited to preserve homeostatic integrity. With further conformational research, electrolyte imbalances may be adopted as effective disease-specific measures of patient safety, such as the proposition of hypercalcemia as one such measure in patients with CKD.¹² Ultimately, this study was aimed at recording levels of calcium, phosphorus, and parathyroid hormone in CKD patients with the interests of assessing the relationship with risk of CVS events depending on the respective serum levels. Unfortunately, there have been many conflicting claims put forth in the past decade regarding the correlation of CV events in CKD patients and the frequency of elevated mineral levels prior; studies evaluating the association of the former with moderate CKD, properly adjusted for confounding variables, is generally sparse.¹³

Table 1: Demographic and clinical profile of patients with and without cardiovascular events

Variable	No CV Events	CV Events	p-value
Age	70.3±10.2	74.3±9.5	0.0085
BMI	30.8±7.14	31.1±7.49	0.7826
HDL	33.7±8.8	35.2±8.5	0.2537
LDL	96.65±33.63	86.13±29.79	0.094
HTN	174 (97.7%)	59 (100%)	0.194
DM	92 (51.69%)	39 (66.10)	0.0489
Hb	12.97±1.54	12.38±1.79	0.0152
GFR	36.61±10.08	32.98±7.03	0.0109

Table 2: The association between iPTH, serum calcium, serum phosphorus and the incidence of cardiovascular events

Variable	No CV Events	CV Events	p-value
iPTH (pg/ml)	108.98±85.63	157.34±106.95	0.0005
Corrected Ca (mg/dl)	9.34±0.42	9.49±0.50	0.2580
Phosphorus (mg/dl)	3.34±0.72	3.57±0.73	0.0351
Ca x Phos. (mg/dl)	31.54±7.7	34.24±7.65	0.0202

Of the demographic factors and clinical profiles, those most significantly associated with the occurrence of cardiovascular events were age, diabetic status, hemoglobin levels, and glomerular filtration rate respectively. Many of these findings seem to coincide with previous studies. The association with age requires little explanation, considering that it is often the determining factor implicated in risk of adverse cardiovascular conditions. Diabetes is another such risk factor, along with smoking and use of blood thinners.¹⁴ A Korean study concerning Hemoglobin concentration and risk of CVD

found a parabolic relationship between levels of hemoglobin and CVD incidence, so any deviation from normal levels was found to increase risk in populations of both males and females.¹⁵ The GFR is a diagnostic tool used to monitor and stage kidney disease such as CKD. The functions of the heart and kidneys are inextricably linked through a multitude of convoluted microsystems regulating homeostasis, such as the renin-angiotensin mechanism. Thus, kidney dysfunction is often directly implicated in many cardiovascular conditions, making the relationship between GFR and CV events understandably conspicuous.³ It is necessary to recognize and adjust for these additional risk factors in order to definitively analyze the independent association of iPTH, calcium, and phosphate with CV events. Despite factoring in the previous risk factors, perhaps of the more counterintuitive findings were that LDL cholesterol levels were lower in patients who experienced CV events and the opposite trend was seen with HDL levels, albeit the difference was statistically insignificant. Due to the action of LDL cholesterol in the production of coronary atherosclerotic plaques thereby increasing the propensity for the development of cardiovascular conditions, it would be expected that higher levels would contribute to CV events by a statistically significant margin; yet the trend was not observed.

In our study it was found that increased levels of iPTH and calcium phosphate product all held statistically significant association with an increased incidence of CVS events. Independent serum calcium levels did not seem to contribute with increased occurrence of CV events. Our findings coincide with an earlier cohort study from the University of Missouri, which concluded that iPTH was a risk factor in moderate chronic kidney disease. In the Missouri study, iPTH was found to be a risk factor independent of calcium phosphate product levels, though both minerals also had a statistically significant association with CV events ($p = .045$).¹² Despite the initial confirmation of our findings, these results seem to be at odds with a meta-analysis conducted over 47 cohort studies published during the span of 1995-2010. The analysis found that consistent, independent association between serum calcium and iPTH levels with respect to the risk of CV events was poor, though serum phosphate was associated with an increased risk of mortality. The evidentiary basis for their conclusion was reached due to supposed low-quality data susceptible to confounding factors and the assumption of a linear relationship.¹⁴ Despite conflicting data, continued research utilizing advanced data collection techniques, more optimally controlled parameters, and the most recent technology may perhaps be able to shed definitive light on the subject and inform healthcare policy respectively.

CONCLUSION

Serum phosphorus and intact iPTH levels were significantly associated with CV events in patients with CKD. Further large scale cohorts can help ascertain these indications more effectively. It is recommended that nephrologists should keep a vigilant eye on these minerals and any disparity must be dealt with promptly albeit cautiously.

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